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Filed : May 19, 2000

### REMARKS

Claims 1, 3, 4, 5, 14 and 28 have been amended. Support for the amendments can be found in the Specification as filed on page 5, lines 30-34, page 7, line 32 to page 8, line 1, page 9, lines 11-12 and page 20, lines 22-27. Support for the amendment to claim 28 can be found in claim 2 as originally filed. As a result, Claims 1, 3-33 are presented for the examination. The following addresses the substance of the Office Action.

#### **Claim rejections under 35 U.S.C. §102**

The Examiner has maintained the rejection of Claims 1, 6, 28 and 33 under 35 U.S.C. §102(e) as being allegedly anticipated by Lockhart et al. (USP 6,344,316). Specifically, the Examiner asserts that Lockhart et al. discloses a method for detecting nucleic acids using an oligonucleotide array, labeling the targets with different means including colloidal gold (see col. 24) and that the target sample is a biological sample (see col. 2, line 34).

M.P.E.P. 2131 requires that, in order to anticipate a claim, the reference must teach every element of the claim. Amended Claim 1 includes the step of "performing a catalytic reduction of a metal present in solution leading to formation of a metallic precipitate in one or more discrete regions." There is no teaching within Lockhart et al. of a method which includes the catalytic reduction of a metal leading to the formation of a metallic precipitate as recited in amended Claim 1. In contrast to the metallic precipitates formed by the catalytic reduction of a metal recited in Claim 1, Lockhart et al. disclose a colorimetric label (e.g. colloidal gold) about 40-80 nm in size and able to scatter green light. Because Lockhart et al. does not disclose catalytic reduction of a metal to form a metallic precipitate, Applicants submit that Lockhart et al. does not anticipate Claim 1.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection to claims 1, 6, 28 and 33 under 35 U.S.C. § 102(e).

#### **Claim rejections under 35 U.S.C. §103**

The Examiner has maintained the rejection of Claims 1, 7-9, and 28 under 35 U.S.C. §103(a) as being allegedly unpatentable over Lockhart et al. (USP 6,344,316) in view of Van Ness et al. (USP 6,027,890). Specifically, the Examiner asserts that one of skill in the art would be motivated to combine Lockhart et al. with Van Ness et al. to arrive at the presently-claimed invention with a reasonable expectation of success. Applicants respectfully disagree.

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In order for a combination of references to render a claim obvious, the combination of references must teach or suggest each of the elements of the claimed invention and must also provide the motivation to combine these elements to create the claimed invention. In *re* Fine, 5 U.S.P.Q.2d 1597 (Fed. Cir. 1988), In *re* Rouffet, 47 U.S.P.Q.2d 1453, 1456 (Fed. Cir. 1998) and In *re* Geiger, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987), In *re* Dembiczak (175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999) As discussed below, the cited combination of references does not suggest all of the elements of the claimed invention, nor does the cited combination of references provide a motivation to combine the elements to create the claimed invention. Furthermore, as discussed below, the claimed invention provides significant advantages over the methods disclosed in the cited references.

As discussed above, Lockhart et al. does not teach or suggest the catalytic reduction of a metal leading to the formation of a metallic precipitate as required by amended Claim 1 of the present invention.

Furthermore, Van Ness et al. does not teach or suggest the catalytic reduction of a metal to form a metallic precipitate. In contrast, Van Ness et al. disclose methods in which a tag is cleaved from a probe and detected using non-fluorescent spectrometry or potentiometry.

Because neither Lockhart et al. nor Van Ness et al. teach or suggest the catalytic reduction of a metal, Applicant maintains that the cited references do not render the claimed invention obvious.

The Examiner has also maintained the rejection of Claims 1, 3-26 under 35 U.S.C. §103(a) as being allegedly unpatentable over Abouzied et al (J. AOAC Internat. 77:495-501) in view of Howard III et al. (EP 0646784) and Van Ness et al. (USP 6,027,890), and further in view of Roth et al. (USP 5,902,727) and Terstappen et al. (USP 5,646,001). More specifically, the Examiner asserts that it would have been obvious for one to combine the techniques of Roth et al., Van Ness et al., and Terstapen et al. with teachings of Abouzied et al. and Howard III et al. to practice the detection of precipitates to take advantage of the increased sensitivity and resolution.

As stated above, the method of amended Claim 1 includes “performing a catalytic reduction of a metal present in solution leading to formation of a metallic precipitate in one or more discrete regions”

The Abouzied et al. reference discloses a colorimetric method of screening and detecting analytes on nitrocellulose (NC) membrane strips. In the method described in Abouzied, a

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colored reaction product formed through the action of an enzyme linked to the target analyte is used to detect the presence of the analyte in the sample. Abouzied does not teach or suggest methods in which a metallic precipitate is formed by the catalytic reduction of a metal. The method of detection includes visually comparing color intensities formed by precipitates on the NC membrane and quantitatively assaying line density using a CCD camera. In addition, in the method disclosed in Abouzied, the lines on the NC membrane strips were spaced 0.25 cm apart (page 496, column 2). As indicated in the specification at page 2, line 32 through page 3, line 11, colorimetric assays in which an enzyme generates a colored reaction product which forms a precipitate, such as the methods described in Abouzied, are unsuitable for use in arrays comprising a density of at least 20 discrete regions per  $\text{cm}^2$  because the precipitate occupies an area which is too large to allow it to be localized to one or more discrete region(s). This is acknowledged in the 2/22/01 Office Action (see page 5) where the Examiner states that "...the dimension of the line blots disclosed does not allow a density of 20 or more discrete regions per  $\text{cm}^2$  with each region having one species of capture molecule..."

With respect to the apparatus of claim 14, Applicants note that Abouzied et al. discloses a nitrocellulose strip being visualized by a camera which is connected to a computer to detect and/or quantify. However, the nitrocellulose strip of Abouzied, as previously discussed, is not a solid support comprising an array of at least 20 discrete regions per  $\text{cm}^2$ . Furthermore, there is no teaching or suggestion Abouzied of a catalytic reduction of a metal to form a metallic precipitate.

Howard III et al. disclose a video test strip reader for detecting the presence of molecules bound to a test strip. The device of Howard is not used to detect a metallic precipitate formed on a high density array as in the present invention but rather to read a signal from a test strip. There is no disclosure or suggestion of detecting the presence of a metallic precipitate formed at one or more discrete region(s) on an array having a density of at least 20 discrete regions per  $\text{cm}^2$  as in the present invention or devices comprising such arrays and such precipitates.

Furthermore, with respect to the apparatus of claim 14, while Howard III et al. discloses a CCD camera equipped with illumination sources and a computer system (see page 5) which can evaluate such information as barcodes. The apparatus disclosed in Howard is used with a test strip rather than an array having a density of at least 20 discrete regions per  $\text{cm}^2$  and does not detect a metallic precipitate formed in one or more discrete region(s).

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With respect to Roth et al., Applicants note that M.P.E.P. 2141.02 cites W.L. Gore & Associates Inc. 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from a claimed invention. Roth discloses a method for localizing and quantitating a molecule in a sample. In the method of Roth, an enzyme generates a colored reaction product which precipitates. However, as discussed above, the precipitate generated through enzymatic reactions is too diffuse to be used with an array having a density of at least 20 discrete regions per  $\text{cm}^2$  as in the present invention.

Roth et al. also disclose the use of antibodies having gold particles fixed thereto along with silver intensification in the context of localizing a molecule in a cell or tissue, a context which is significantly different than the microarrays utilized in the present invention. In addition, Roth et al. teach that methods using gold particles and silver intensification are undesirable or labor intensive in quantitative analyses (see Column 1, line 24-30). Accordingly, Roth et al. teach away from methods in which a metallic precipitate is used and therefore, as stated in M.P.E.P. 2141.02, does not teach or suggest the claimed invention.

Terstappen et al. disclose the use of magnetic beads to collect cells, specifically for separation of a target molecule. However, there is no disclosure or suggestion in Terstappen et al. of detecting nucleic acids by the presence of a metallic precipitate in one or more discrete regions formed by a catalytic reduction on an array having a density of at least 20 discrete regions per  $\text{cm}^2$  as in the present invention or devices comprising such arrays and such precipitates.

Because the combination of the cited references does not teach or suggest the claimed invention, Applicants respectfully submit that claims 1, and 3-26 are non-obvious in view of the above-combination of references.

The Examiner has rejected claims 27, and 29-32 under 35 U.S.C. §103(a) as being allegedly unpatentable over Abouzied et al. (J. AOAC Internat. 77:495-501) in view of Van Ness et al. (USP 6,027,890), and Gingeras et al. (USP 6,228,575). Specifically, the Examiner states that it would have been obvious to one of skill in the art such that a CCD camera would have been linked to a computer with a program to recognize such images of discrete regions on the array in order to process the images taken by the camera, and to detect/quantitate the target compounds. The Applicant respectfully disagrees.

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As discussed above, Claim 14 (of which the rejected claims are dependent upon) recites metallic precipitates formed by catalytic reduction of a metal. Neither of the cited references teach or suggest the recited metallic precipitates formed by catalytic reduction of a metal.

Therefore, the combination of cited references does not render the claimed invention obvious since they do not teach or suggest the invention as presently claimed.

Objective evidence of unexpected results relevant to issue of obviousness

According to M.P.E.P. 2141, objective evidence of unexpected results is relevant to the issue of obviousness. Applicants submit that the Declaration of Jose Remacle, dated November 19, 2001, provides objective evidence of unexpected results utilizing the method of the present invention. In particular, as provided in the Declaration dated Nov. 19, 2001, the metallic precipitates result in an improvement in sensitivity of over 1000-fold with respect to the methods disclosed in Van Ness (see Exhibit B, demonstrating that the limit of detection of spotted DNA for the metallic precipitate used in the present invention was 0.1 nM, while the peroxidase-based methods of Van Ness had a detection level of 100 nM). In addition, as provided in the Declaration, the metallic precipitates utilized in the present invention may be detected in a matter of minutes as opposed to the several hours required to detect the precipitates in the methods of Van Ness (see Exhibit C demonstrating that the metallic precipitate was obtained in 10 minutes as opposed to the peroxidase precipitate, which was formed after 3 hours). The high sensitivity and short reaction time are extremely beneficial in high throughput methods performed on high density arrays.

Furthermore, in the methods disclosed in Van Ness et al., the spots formed by the non-metallic precipitate resulting from the enzymatic reaction have a diameter of 50 micrometers. Such dimensions are not compatible with the high density arrays utilized in the present methods as they would not permit the differentiation of adjacent regions. In contrast, the metallic precipitates formed in the methods of the present invention may readily be localized to a single position on the high density arrays used in the methods of the present invention.

Applicants provide herewith an additional Declaration by Jose Remacle, dated November 5, 2002, further demonstrating the advantages of the methods of the present invention. This Declaration was originally provided with the Amendment submitted November 5, 2002 which was not entered. In particular, the accompanying Declaration demonstrates that the catalytic reduction of a metal to form a metallic precipitate provides a significant amplification of the

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signal relative to methods employing gold particles alone. In addition, the accompanying Declaration demonstrates that the present methods permit detection using infra-red light, thereby providing an enhanced signal/noise ratio relative to methods which employ visible light.

In view of the above remarks and accompanying Declaration, Applicants respectfully request withdrawal of the rejection to claims under 35 U.S.C. § 103(a).

### CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are inapplicable to the present claims. Accordingly, Applicants request the expeditious allowance of the pending claims.

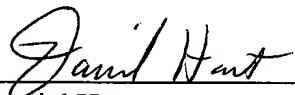
The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned at (619) 687-8633 (direct line), to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: June 15, 2009

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